Clin Chem Lab Med 2009;47(10):1227–1231 © 2009 by Walter de Gruyter • Berlin • New York. DOI 10.1515/CCLM.2009.276

Polymorphisms of the β1-adrenergic receptor gene are associated with essential hypertension in Chinese

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Abstract

Background: The β1-adrenergic receptor (ADRB1) plays a pivotal role in mediating signal transduction of the sympathetic-adrenal system, which is involved in the regulation of cardiac output and peripheral resistance. Our goal was to determine whether the polymorphisms Arg389Gly (rs1801253) and Ser49Gly (rs1801252) of the *ADRB1* gene were associated with essential hypertension in Chinese.
Methods: We tested our hypothesis in two independent case-control studies, one comprised 481 patients with hypertension and 529 control subjects, and the other study comprised 212 patients and 325 control subjects. All subjects were genotyped for Arg389Gly and Ser49Gly polymorphisms.
Results: The first study showed that the Arg389Arg genotype of the *ADRB1* gene was associated with risk of hypertension [odds ratio (OR) 1.77, 95% confidence interval (CI) 1.09–2.98; $p=0.008$], and the association was replicated in the second independent population (OR 1.65, 95% CI 1.07–2.89, $p=0.01$). The patients with the Arg389Arg genotype had significantly higher diastolic blood pressure (DBP) than did those with Arg389Gly genotype as well as those with Gly389Gly genotype (100.29 ± 11.01 mm Hg vs. 95.33 ± 13.10 mm Hg and vs. 96.17 ± 12.18 mm Hg, respectively, $p=0.01$, $p=0.02$). The association was replicated in the second study (103.7 ± 13.3 mm Hg vs. 97.31 ± 12.9 mm Hg and vs. 96.29 ± 13.4 mm Hg, respectively, $p=0.03$, $p=0.02$). Heart rate also showed an association (in first study: 79.43 ± 9.90 bpm vs. 74.87 ± 8.96 bpm, vs. 73.92 ± 8.18 bpm, respectively, $p=0.02$, $p=0.014$; in the second study: 81.12 ± 8.99 bpm vs. 74.85 ± 7.97 bpm and vs. 73.89 ± 9.12 bpm, $p=0.007$, $p=0.006$, respectively). No association was seen between systolic blood pressure (SBP) and any of the three genotypes at amino acid position 389 in hypertensive patients, neither between the Ser49Gly polymorphisms and hypertension, nor between the Ser49Gly genotypes and DBP and heart rate.
Conclusions: The polymorphisms of the *ADRB1* gene were associated with essential hypertension. The Arg389Gly polymorphism of the *ADRB1* gene confers higher risk for hypertension.
Clin Chem Lab Med 2009;47:1227–31.

Keywords: β1-adrenergic receptor; Chinese population; essential hypertension; polymorphism.

Introduction

Essential hypertension (EH) is a multifactorial disease with a substantial genetic component (1, 2). It has been reported that the role of genetic factors responsible for blood pressure is estimated as being up to 30%–50% (3). Blood pressure is determined by two factors: cardiac output and peripheral resistance, which are regulated by the sympathetic nervous system (4). The β1-adrenergic receptor (ADRB1) plays a pivotal role in mediating signal transduction in the sympathetic-adrenal system.

The human ADRB1 is a member of the family of seven-transmembrane G-protein-coupled receptors, and expressed in cardiac myocytes (5). The *ADRB1* gene was cloned in 1987, and localized to chromosome 10 (6). In the *ADRB1* coding region, two single nucleotide polymorphisms (SNPs) have been identified (7). The Arg389Gly polymorphism is located in the intracellular cytoplasmic tail near the 7th transmembrane region of the receptor, which is a putative Gs-protein binding domain. The Arg389 variant mediates higher isoproterenol-stimulated adenylate cyclase activity than the Gly389 variant in vitro (8). The Ser49Gly polymorphism is located in the extracellular amino-terminal region of the receptor (Ser-to-Gly substitution) (9). A previous study has shown that the Gly49 *ADRB1* displays more profound agonist-promoted down-regulation compared with the Ser49 *ADRB1* variant (10). In cells expressing Gly49 *ADRB1*, both basal and agonist stimulated adenylyl cyclase activities are also higher than in cells expressing the Ser49 variant (Ser49 *ADRB1*) (11). These experimental results suggest that polymorphism in the *ADRB1* gene (Arg389Gly and Ser49Gly) might have important biological significance in the pathogenic process of hypertension.

The goal of the present study was to investigate whether the functionally important Arg389Gly polymorphism or the Ser49Gly polymorphism of the *ADRB1* gene was associated with hypertension. The results obtained from the first population were replicated in another independent population of hypertensive subjects.

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Received March 1, 2009; accepted July 8, 2009; previously published online September 11, 2009

Materials and methods

Subjects

The subjects of the first study were comprised of outpatients from a hospital in Shijiazhuang city, Hebei province, People's Republic of China. The subjects consisted of 481 patients with mild and moderate EH, and age- and gender-matched controls (529) from the same area. According to World Health Organization (WHO) criteria (12), patients were defined as being hypertensive if they had systolic blood pressure (SBP) and/or diastolic blood pressure (DBP) $\geq$140/90 mm Hg on three occasions within 2 months and not taking anti-hypertensive treatment, and/or if they had been diagnosed as being hypertensive in the past and were currently receiving anti-hypertensive medications. Patients were excluded if they had renal disease, secondary hypertension, atrio-ventricular conduction block, chronic obstructive bronchitis, bronchial asthma, chronic myeloproliferative diseases, diabetes, hypertrophy cardiomyopathy, valvular heart diseases, pulmonary hypertension, coronary heart disease or heart failure. Blood pressure was measured by the same investigator using the right arm with a mercury sphygmomanometer and standard techniques after at least 5 min of rest in a sitting position.

The controls were recruited from age- and gender-matched healthy subjects from the same city. They had no history or symptoms of cardiovascular diseases. All participants were of the Han ethnic group. Informed consent was obtained from all individuals.

In the second study, the population was from a community center in Beijing Fengtai District. The study population was comprised of 212 cases with hypertension and 325 control subjects and was recruited using the same criteria as the first study. The study was approved by the Ethics Committee of the Hebei Provincial People's Hospital and the participating hospital.

Determination of biochemical variables and clinical data collection

Blood samples were collected following a 12-h overnight fast. All samples were analyzed for serum sodium, potassium, creatinine, uric acid, blood urea nitrogen (BUN), total plasma cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and blood glucose within 3 months using an automated analyzer (Hitachi 7060, Hitachi, Tokyo, Japan). A complete medical history was obtained from all subjects, including family history of hypertension, diabetes mellitus, and the following cardiovascular risk factors, alcohol intake, cigarette smoking, family history of coronary heart disease or stroke, weight, height, body mass index (BMI), SBP, and DBP. BMI was calculated using the formula of weight (kg)/height (m^2). A complete clinical history was obtained from all subjects.

Genotyping of Arg389Gly and Ser49Gly

Peripheral blood (10 mL) was collected into tubes containing trisodium citrate (final concentration in blood, 0.026 mol/L), and centrifuged at 3000 *g* for 10 min at room temperature. The plasma and ''buffy-coat'' were separated and stored in a 1.5-mL EP tube at –70°C. All assays were performed in duplicate. DNA was extracted from the ''buffy-coat'' as described previously (13), and stored at –70°C before use.

Single nucleotide polymorphism Arg389Gly was analyzed by amplification of a 530-base pair (bp) sequence with primers: 5′-CGC TCT GCT GGC TGC CCT TCT TCC -3′ and 5′-TGG GCT TCG AGT TCA CCT GCT ATC-3′ (6). The polymerase chain reaction (PCR) products were digested with BcgI (New England Biolabs, Beverly, MA, USA); only one band for the Gly389Gly homozygote, two DNA fragments of 376 bp and 154 bp were obtained for the Arg389Arg homozygote on 3% agarose gel and three bands for the Arg389Gly heterozygote.

The Ser49Gly polymorphism was amplified using PCR with the following primers: 5′-CCGGGCTTCTGGGGTGTTCC-3′ and 5′-GGCGAGGTGATGGCGAGGTAGC-3′ (6). The resultant PCR products of 562 bp were digested with Eco0109I (New England Biolabs, Beverly, MA, USA). Only one band for the Ser49Gly homozygote, two DNA fragments of 342 bp and 220 bp were obtained for the Gly49Gly homozygote on 3% agarose gel, and three bands for the Ser49Gly heterozygote.

The sequence was confirmed by bidirectional sequencing of 200 samples with ABI Prism 3730 Genetic Analyzer (Applied Biosystems Inc.) (14), and the reproducibility was 100%.

Data are expressed as mean $\pm$ standard deviation (SD). The χ^2-test was used for testing categorical variables, the Hardy-Weinberg equilibrium of the polymorphisms, and genotype/allele frequencies. Quantitative variables between groups were tested with Student's test. The association of SNPs with hypertension was analyzed using multivariate logistic regression. The analysis was adjusted for age, gender, BMI, smoking, alcohol consumption, glucose, HDL-C, LDL-C, TC, TG and family history of hypertension. A two-tailed $p < 0.05$ was considered significant. Statistical analysis was performed with the SPSS 13.0 package. A SHEsis software platform (http://analysis.bio-x.cn/myAnalysis.php) was used to analyze pairwise linkage disequilibrium (LD) (15). The D′ and r^2 were used to indicate the strength of LD.

Results

Characteristics of the subjects

The characteristics of patients and control subjects are shown in Table 1. The levels of SBP, DBP, TG, glucose and LDL-C were significantly higher in hypertensive patients than in controls. No differences in BMI, TC or heart rate were found between cases and controls.

Genotype distributions of Ser49Gly and Arg389Gly polymorphisms

The distributions of Gly389Gly, Arg389Gly and Arg389Arg genotypes of the *ADRB1* polymorphism are shown in Table 2. They were in agreement with Hardy-Weinberg equilibrium for both cases and controls. The frequency of the Arg389Arg genotype was significantly higher in hypertensive patients than in controls. The association remained after adjustment for age, gender, and other conventional risk factors with multiple logistic regression analysis in the two independent populations (Table 2, Figure 1).

The distributions of Ser49Gly genotypes frequencies are summarized in Table 2. They were in agreement with Hardy-Weinberg equilibrium for both cases

Table 1 Clinical characteristics.

Variables	First population		Second population	
	Hypertension (n=481)	Controls (n=529)	Hypertension (n=212)	Controls (n=325)
Age, years	55.45±10.80	54.69±10.43	56.31±11.12	55.28±10.61
Gender, male (%)	53.56	50.81	54.14	52.36
BMI, kg/m^2	25.09±2.63	24.80±2.63	26.17±2.49	22.98±2.18
SBP, mm Hg	158.44±18.67[a]	120.4±12.4	160.12±17.89[a]	117.4±11.3
DBP, mm Hg	97.3±12.1[a]	78.5±7.2	99.1±13.2[a]	76.9±8.1
HDL-C, mmol/L	1.36±0.20[b]	1.46±0.29	1.35±0.18[b]	1.48±0.31
LDL-C, mmol/L	2.98±0.54[b]	2.78±0.77	3.02±0.67[a]	2.67±0.59
TC, mmol/L	4.73±0.93	4.95±1.09	4.82±0.89	4.79±0.98
TG, mmol/L	1.68±0.42[b]	1.35±0.51	1.72±0.51[b]	1.34±0.49
Glucose, mmol/L	5.32±1.48[b]	4.74±1.25	5.51±1.39[b]	4.66±1.39
Heart rate, beats min^{-1}	76.07±9.02	73.27±7.91	76.62±8.68	72.89±8.23
Drinking, %	23	21.6	24.2	20.9
Smoking, %	24.6	23.1	25.1	21.2
Family history of hypertension, %	30[b]	15.2	26[b]	13

[a]Hypertensive patients vs. controls $p<0.01$. [b]Hypertensive patients vs. controls $p<0.05$. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total plasma cholesterol; TG, triglyceride.

Table 2 Distribution of the *ADRB1* Ser49Gly polymorphisms in hypertensive patients and controls.

Groups	Arg389Gly genotype			Ser49Gly genotype		
	Arg/Arg	Arg/Gly	Gly/Gly	Gly/Gly	Gly/Ser	Ser/Ser
First population						
Hypertensive patients, n (%)	249 (51.8)[a]	197 (40.9)	35 (7.3)	321 (66.8)	146 (30.2)	14 (3)
Controls, n (%)	245 (46.3)	232 (43.9)	52 (9.8)	360 (68.0)	156 (29.5)	13 (2.5)
Second population						
Hypertensive patients, n (%)	112 (53)[a]	81 (38.2)	19 (8.8)	138 (64.9)	67 (31.6)	7 (3.5)
Controls, n (%)	149 (45.8)	143 (44.1)	33 (10.1)	218 (67.1)	93 (28.7)	14 (4.2)

χ^2-test vs. control or hypertensive patients. [a]$p<0.05$.

and controls. No statistically significant differences in Ser49Gly genotypes frequencies were found with the χ^2-test in hypertensive patients and controls (Table 2). Any association between the Ser49Gly polymorphism and hypertension was not found in the two independent populations.

Arg389Gly and Ser49Gly polymorphism and clinical phenotypes

In the first study population, 249 (51.8%) patients were homozygous for the Arg389allele, 197 (40.9%) patients were heterozygous, and 35 (7.3%) patients

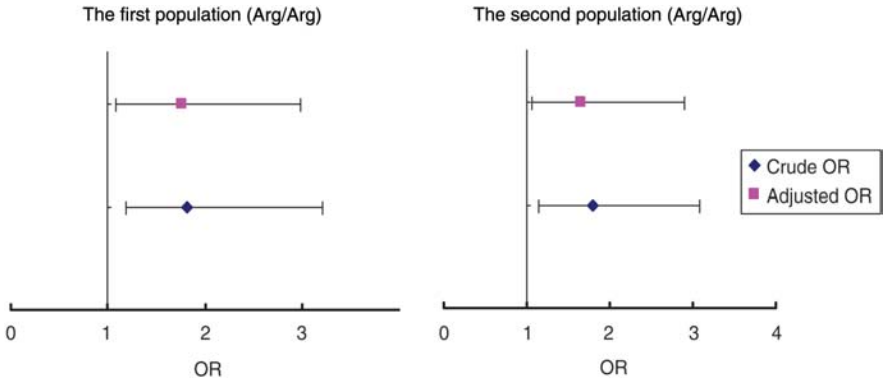

Figure 1 Association of the *ADRB1* Arg389Gly polymorphism with hypertension.
The odds ratio (OR) of the Arg389Arg genotype in the first population was 1.77 [95% confidence interval (CI) 1.09–2.98; $p=0.008$]. The OR in the second independent population was 1.65 [95% CI 1.07–2.89, $p=0.01$]. OR and 95% CI were calculated using multivariate logistic regression analyses. Adjusted OR were stratified by age, gender, body mass index, systolic blood pressure, diastolic blood pressure, glucose, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglyceride; total plasma cholesterol; family history of hypertension.

Table 3 Clinical characteristics according to Arg389Gly and Ser49Gly of the *ADRB1* polymorphism genotypes in hypertensive patients.

Variables	First population			Second population		
	Arg/Arg, n = 249 (51.8%)	Arg/Gly, n = 197 (40.9%)	Gly/Gly, n = 35 (7.3%)	Arg/Arg, n = 112 (53%)	Arg/Gly, n = 81 (38.2%)	Gly/Gly, n = 19 (8.8%)
Arg389Gly						
Age, years	55.38 ± 10.71	56.09 ± 11.03	54.89 ± 10.44	57.94 ± 10.28	53.31 ± 10.76	57.68 ± 12.31
Gender, male, %	51.50	54.29	52.76	54.05	51.98	56.39
SBP, mm Hg	160.50 ± 19.38	157.24 ± 19.40	157.58 ± 17.23	158.74 ± 18.45	159.21 ± 18.33	162.41 ± 16.89
DBP, mm Hg	100.29 ± 11.01	95.33 ± 13.10[a]	96.17 ± 12.18[a]	103.7 ± 13.3	97.31 ± 12.9[a]	96.29 ± 13.4[a]
Heart rate, beats min^{-1}	79.43 ± 9.90	74.87 ± 8.96[a]	73.92 ± 8.18[a]	81.12 ± 8.99	74.85 ± 7.97[a]	73.89 ± 9.12[a]
	Gly/Gly, n = 321 (66.8%)	Gly/Ser, n = 146 (30.2%)	Ser/Ser, n = 14 (3%)	Gly/Gly, n = 138 (64.9%)	Gly/Ser, n = 67 (31.6%)	Ser/Ser, n = 7 (3.5%)
Ser49Gly						
Age, years	54.84 ± 10.55	55.62 ± 11.23	55.9 ± 10.38	56.26 ± 11.99	57.98 ± 11.23	54.78 ± 10.13
Gender, male, %	53.9	52.54	52.1	54.96	53.18	54.27
SBP, mm Hg	160.5 ± 18.16	157.4 ± 16.32	156.9 ± 21.45	160.18 ± 18.44	158.79 ± 18.33	161.38 ± 16.89
DBP, mm Hg	98.18 ± 10.67	98.44 ± 11.52	95.20 ± 13.88	99.03 ± 13.24	98.29 ± 13.43	99.97 ± 12.91
Heart rate, beats min^{-1}	73.89 ± 7.20	76.91 ± 9.20	77.51 ± 10.45	77.85 ± 7.71	77.88 ± 8.81	74.12 ± 9.42

[a]The difference is significant at $p < 0.05$. SBP, systolic blood pressure; DBP, diastolic blood pressure.

were homozygous for the Gly389 allele. In the second study population, 53% were homozygous for Arg389Arg, 38.2% were heterozygous for the Arg389Gly, and 8.8% homozygous for Gly389Gly. Hypertensive patients carrying Arg389Arg variants had significantly increased DBP and heart rate by one-way ANOVA analysis. However, no difference was found in SBP among the three genotypes of Arg389Gly in the two populations (Table 3).

No difference was identified in clinical variables (including SBP, DBP and HR) among the three genotypes of Ser49Gly in hypertensive patients in the two populations using one-way ANOVA (Table 3).

Linkage disequilibrium analysis

LD was performed between the Arg389Gly and Ser49Gly using the standard definition of D′ and r^2. We found that the two SNPs were not in LD with $D' = 0.26$ and $r^2 = 0.04$, indicating that the two SNPs were not in a same natural haplotype block.

Discussion

The present study found that the Arg389Gly polymorphism of *ADRB1* is associated with hypertension in Chinese. Hypertensive patients with Arg389Arg variants had significantly increased DBP. This is the first investigation to test the association between Arg389Gly or Ser49Gly *ADRB1* polymorphisms with hypertension in two independent populations. This finding is consistent with the results reported by Bengtsson et al., where individuals homozygous for the Arg389 allele of the *ADRB1* gene were at increased risk of developing hypertension (16). Shioji et al. reported that the prevalence of the Gly389 *ADRB1* variant was significantly lower in hypertensive compared with normotensive patients, which also supports our result (17). Karlsson reported that the Ser49Gly *ADRB1* polymorphism had no effect on basal hemodynamics in hypertensive patients (18). However, some inconsistent results have been reported showing that the prevalence of the Arg389Gly and the Ser49Gly *ADRB1* polymorphisms in hypertensive patients was not different from that in normotensive subjects from the same region (19). Several reasons might explain the discrepancies between these studies. First, the frequencies of genotypes, alleles, haplotypes and LD pattern may differ between various ethnic groups. Second, the different prevalence and clinical feature of hypertension in different ethnic populations can affect the results of the association study (20). Our study also found that patients with the Arg389Arg genotype had a higher heart rate than those that were either homozygous or heterozygous for Gly389, suggesting that the receptor variant Arg389Arg had higher sensitivity in response to catecholamines. Homozygous subjects for the Arg389 allele showed an increase in response to stimulation of the β1-adrenergic receptor by catecholamines.

In vitro studies have shown that the Arg389 variant of the *ADRB1* gene mediates an increased response

to agonist stimulation compared with the Gly389 variant. This suggests that the Arg389Gly polymorphism is of functional importance. The Arg389 variant exhibited slightly higher basal adenylyl cyclase activity than the Gly389 variant. In addition, isoprenaline-induced adenylyl cyclase activation was about 3–4 times greater in Arg389 than in Gly389 *ADRB1* cells. This may be due to a reduction in the beta-AR-Gs protein coupling for the Gly389 *ADRB*1 (7, 21). Similar results have been obtained in cells expressing the Arg389 *ADRB1* or Gly389 *ADRB1*, where the maximal increase in cyclic adenosine monophosphate caused by isoprenaline was significantly larger in Arg389 than in Gly389 *ADRB1* cells (22). The increased in vivo activity of the Arg389 variant of *ADRB1* could be expected to lead to higher cardiac output, and could therefore explain the association between the Arg389 allele and hypertension in our study. This may also partially explain our results that Arg389Gly polymorphism conferred a higher risk of hypertension.

The strength of our study is that the result was completely replicated in another independent population, remote from the first population. The subjects in the present study were all of Han ethnic group to control for population stratification. In addition, we selected hypertensive patients with a relatively early age at onset, and control subjects without a family history of hypertension to avoid selection bias of patients and controls. However, some limitations must be considered. The sample size can affect the consequences of an association study. Therefore, our results need to be confirmed in a larger sample of individuals.

In conclusion, our findings suggest that the Arg389Arg genotype of the *ADRB1* gene confers an increased risk for development of hypertension.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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